**Plasmodium Falciparum (malaria)**

Presentation:

1. A 9-year-old boy was brought to the hospital by his parents with complaints of repeating intense chills and daily high fever for 4 days. The parents said that when his fevers would abate, he would become drenched in sweat and feel exhausted and drained. The parents also reported diarrhea, nausea, and abdominal pain. On the day of admission the patient was noted to be lethargic and difficult to arouse. A generalized seizure was witnessed in the emergency department. The family had immigrated to the United States from West Africa 3 weeks before the onset of the current illness.
2. PE
   1. Thin male minimally responsive to verbal commands. Pupils were reactive and neck was supple. Conjunctiva was pale, and abdominal exam showed hepatosplenomegaly.

Plasmodium Falciparum (malaria):

1. Plasmodia are coccidian protozoal agents.
2. The four human-infective species
   of Plasmodium are P. falciparum, P. vivax, P. malariae, and P. ovale.
   1. Only P. falciparum causes life-threatening infection.
3. The most salient morphologic characteristics of plasmodia belong to the following four developmental stages:
   1. 1. Ring.
      1. Early developmental stage of the asexual erythrocytic parasite, often arranged in a **ring shape around a central vacuole**
   2. 2. Trophozoite.
      1. parasite has lost its “ring” appearance and has begun to accumulate pigment.
      2. The trophozoite of P. vivax is **ameboid** in shape, and the **enlarged infected erythrocyte contains numerous “Schüffner dots”**
   3. 3. Schizont.
      1. the parasite has begun its division into merozoites and thus is characterized by the presence of multiple contiguous chromatin dots.
   4. 4. Gametocyte.
      1. Sexual erythrocytic stages (female is the macrogametocyte and male is the microgametocyte).

Epidemiology:

1. global problem, with an estimated 300 to 500 million cases occurring annually.
2. Forty-one percent of the world’s population lives in areas where malaria is transmitted.
3. Geographic boundaries are dictated by the presence of the Anopheles mosquito vector.
4. P. vivax and P. falciparum account for more than 95% of all reported cases.
5. P. malariae accounts for 4% of cases, and P. ovale is extremely rare.
6. P. falciparum infection is more severe and life-threatening and requires more aggressive therapy.
7. Children and the elderly are at particular risk.
8. Blacks are less susceptible than are whites.
9. The absence of the Duffy (a red cell antigen) gene in the West African population is responsible for low incidence of vivax malaria.
10. Sickle-cell trait also provides protection from malaria because RBCs in
    sickle-cell trait are not able to support growth of the organism.
    1. A higher incidence of sickle-cell trait is found in populations where malaria is endemic.

Pathogenesis

1. During a blood meal, a Plasmodium-infected female Anopheles mosquito inoculates sporozoites into the human host, beginning a complex cycle of replication.
2. Sporozoites infect liver cells (asexual stage) and mature into schizonts, which transform into merozoites that are released from the liver to invade red blood cells (RBCs) and attach themselves to specific binding sites on RBCs (Duffy blood group antigen for P. vivax entry and a glycophorin antigen for P. falciparum).
3. Within erythrocytes, merozoites feed on hemoglobin and other proteins, maturing into trophozoites. Trophozoites undergo nuclear division (without cell division) to form 16 to 32 parasite nuclei (schizonts) within a single RBC.
4. Eventually, the RBC ruptures, and schizonts pinch off to form new merozoites, which infect new RBCs, and the erythrocytic cycle repeats.
5. At some point, the parasites (micro- and macrogametocytes) may be taken up by the vector mosquito, where they undergo sexual stages in the midgut of the mosquito to form sporozoites that can be released once more into a human host.
6. Severity of malaria depends on the age and immune status of the patient and also on the species of parasite (e.g., P. falciparum is the most virulent). One brood of parasites becomes dominant and is responsible for the synchronous nature of the clinical symptoms of malaria (cyclic paroxysms). This protozoan brood replication inside the cell induces RBC cytolysis, causing the release of toxic metabolic byproducts into the bloodstream as many RBCs rupture at the same time (the host experiences flu-like symptoms).
7. Anemia results from the lysis of infected RBCs, the suppression of
   hematopoiesis, and the increased clearance of RBCs by the spleen. Over time, malaria infection causes thrombocytopenia.
8. Hepatosplenomegaly is due to an influx of host cells.
9. Plasmodium falciparum infects all RBCs (young, middle-aged, or old), thus the level of parasitemia is higher than with other Plasmodium species.
10. Because more merozoites are produced, more RBCs are destroyed, and a lack of O2 for body tissues becomes a problem.
11. The parasites derive their energy solely from glucose, and they metabolize it 70 times faster than do the RBCs they inhabit, thereby causing hypoglycemia and lactic acidosis.
12. The dominant (persistent) hepatic stage (hypnozoites) of P. vivax and P. ovale may persist in the liver of infected individuals, emerging at a later time and requiring additional drug treatment to prevent malaria relapse. Immunologic response to malaria is hard to assess and may involve both antibody-mediated and cell-mediated immunity. A period of time away from exposure is sufficient for the immunity to wane in an exposed person from a highly endemic area.

Diagnosis

1. Lumbar puncture and CSF examination to rule out bacterial meningitis
2. Blood cultures to detect blood-borne bacteria
3. Thick and thin smear for blood-borne parasites
4. In failed diagnosis, virus-specific serology for the listed infections
5. Laboratory diagnosis is made by demonstration of the parasite within red blood cells. The types of smears obtained are
   1. 1. Thick film.
      1. RBCs are lysed, and WBC, platelets, and parasites are visible.
      2. This screening method does not differentiate Plasmodium from Babesia.
   2. 2. Thin film.
      1. With this method, morphologic features are visible for differentiation of Plasmodium from Babesia and for definitive species identification.
6. The following factors are helpful in determining parasite species:
   1. Number of intraerythrocytic parasites (multiplicity/ cell).
   2. Morphologic characteristics of the parasites (e.g., crescent-shaped gametocyte in P. falciparum)
   3. Degree of parasitemia (number of infected erythrocytes in a blood film)
      1. heavy is considered to be greater than or equal to 10% (with P. falciparum [usually seen in severe malaria]).
7. Microscopists may, however, occasionally fail to differentiate between species in cases in which morphologic characteristics overlap (especially P. vivax and P. ovale), as well as in cases in which parasite morphology has been altered by drug treatment or improper storage of the sample. In such cases, the Plasmodium species can be determined by using confirmatory molecular diagnostic tests (e.g., PCR).

Differential Dx:

1. African trypanosomiasis (sleeping sickness)
2. Aseptic meningitis
3. Babesiosis
4. Bacterial meningitis
5. Dengue fever
6. Leptospirosis
7. Malaria
8. Typhoid fever

Treatment / Prevention:

1. Treatment
   1. Treatment varies according to the infecting species, the geographic area where the infection was acquired, and the severity of the disease. There are three “r” problems associated with management of malaria
      1. 1. In recrudescence
         1. a controllable number of parasites remains in the blood stream (latent in RBC) because of inadequate immune response or antimalarial therapy; parasites reactivate on physical trauma or immunosuppression.
      2. 2. In relapse
         1. sporozoites are dormant in liver and reactivate; dormant sporozoites are referred to as hypnozoites (common with vivax malaria)
      3. 3. In resistance
         1. antimalarial drugs become ineffective.
   2. Chloroquine remains the drug of choice if the patient is infected with a susceptible strain of Plasmodium species
   3. Intrahepatic organisms, such as the hypnozoites of vivax/ovale, are not killed by chloroquine; they are killed by primaquine (which must be used to prevent relapses).
   4. For chloroquine-resistant strains (usually P. falciparum), drugs such as mefloquine, Malarone (a combination of atovaquone and proguanil), quinine (or intravenous quinidine), or an artemisinin derivative, can be used for successful treatment.
   5. Doxycycline or clindamycin may be used in combination with the drugs for P. falciparum. In severe cases of falciparum malaria, exchange transfusion is recommended to rapidly reduce the level of parasitemia.
2. Prevention
   1. The key to prevention is avoidance of mosquito exposure in endemic areas. Use of netting at night and repellent spray with DEET is helpful. However, chemoprophylaxis is usually recommended for travelers to further reduce risk. Chloroquine is effective, although in many areas of the world endemic for malaria, P. falciparum is resistant to this drug. In these areas, mefloquine is usually recommended, although doxycycline and atovaquone/proguanil are also effective. Unfortunately, a vaccine is not available, although much research work is being done in this area.